

U.S. Patent Application No. 10/691,186  
Response to Notice of Non-Compliant Amendment and Corrected Amendment  
and Reply dated December 26, 2006  
In Response to Notice of Non-Compliant Amendment Dated December 18, 2006

**AMENDMENTS TO THE CLAIMS:**

This listing of claims will replace all prior versions, and listings, of claims in the application:

**Listing of claims:**

1-218. (Canceled)

219. (Previously presented) An apparatus, comprising:

a heating and cooling system,

a sample block including at least one well for at least one sample tube containing a known volume of a liquid sample mixture wherein the sample block is capable of thermal contact with the heating and cooling system,

means for determining the temperature of said block in a first sample interval, wherein said first sample interval is an interval of time designated as time  $n$ ; and

a computing apparatus to control the heating and cooling system and comprising a program adapted to determine the temperature of a liquid sample mixture as a function of the temperature of said sample block over time by utilizing the relationship:

$$T_{\text{samp}_n} = T_{\text{samp}_{n-1}} + (T_{B_n} - T_{\text{samp}_{n-1}}) * t_{\text{interval}} / \tau$$

where  $T_{\text{samp}_n}$  is equal to the sample temperature in said first sample interval,  $T_{\text{samp}_{n-1}}$  is a sample temperature in a second sample interval immediately preceding the first sample interval, said second sample interval designated as time  $n-1$ ,  $T_{B_n}$  is equal to the block temperature in said first sample interval,  $t_{\text{interval}}$  is a time in seconds between consecutive sample intervals, and  $\tau$  is a function of thermal characteristics of said apparatus.

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220. (Previously presented) The apparatus of claim 219, wherein said thermal characteristics comprise a first thermal time constant corresponding to at least one sample tube and a volume of a sample mixture, and a second thermal time constant corresponding to a block temperature sensor thermally coupled to said block, and tau equals approximately said first thermal time constant minus said second thermal time constant.

221. (Previously presented) The apparatus of claim 219, further comprising an input device for receiving user defined setpoints defining a hold time/temperature profile, wherein said computing apparatus includes a controller capable of controlling said heating and cooling system as a function of said user defined setpoints and a sample temperature.

222. (Previously presented) The apparatus of claim 219, wherein the at least one well of the sample block is capable of receiving at least one sample tube containing a volume of liquid sample mixture in the range of from approximately 20 microliters to approximately 100 microliters.

223. (Previously presented) The apparatus of claim 219, further comprising an enclosure for said sample block, said enclosure defining an enclosed ambient atmosphere, and wherein said sample block comprises a central region, an end edge region, and a manifold region, the central region comprises an upper surface, the upper surface contains an array of sample wells for holding the at least one sample tube, the end edge region comprises two end edges at opposite ends of said block which are in thermal contact with said enclosed ambient atmosphere, and the

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manifold region comprises two manifold edges at opposite sides of said block, wherein each said manifold edge is thermally coupled to a manifold.

224. (Previously presented) The apparatus of claim 223, wherein said heating and cooling system includes a heater having a central heating zone thermally coupled to the central region, an end edge heating zone thermally coupled to the end edge region, and a manifold heating zone thermally coupled to the manifold region.

225. (Previously presented) The apparatus of claim 224, wherein said computing apparatus comprises means for determining an actual heating power to be applied to each said heating zone in said first sample interval, including:

means for determining a theoretical second power representing the total power to apply to said block in said sample interval, without accounting for power losses,

means for determining theoretical third powers to be applied to each said zone in said first sample interval as a function of said theoretical second power,

means for determining power losses by said regions in said first sample interval, and

means for determining the actual heating power to be applied to each said heating zone as a function of said theoretical third powers and said power losses by said regions.

226. (Previously presented) The apparatus of claim 224, wherein said sample block contains multiple transverse bias cooling channels alternating with multiple transverse ramp cooling channels, said bias and ramp cooling channels being parallel to said upper surface, said system further comprising means for constantly pumping chilled coolant through said bias cooling

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channels and means for selectively pumping chilled coolant through said ramp cooling channels and comprising valve means controlled by said computing apparatus.

227. (Previously presented) The apparatus of claim 226, wherein said computing apparatus comprises means for determining a total cooling power to be applied to said block in said first sample interval including:

means for determining a theoretical cooling power representing the total power to apply to said block in said first sample interval without accounting for power losses,

means for determining power losses in said block regions in said first sample interval, and

means for determining said total cooling power as a function of said theoretical cooling power and said power losses.

228. (Previously presented) The apparatus of claim 227, wherein said means for selectively pumping chilled coolant through said ramp cooling channels further comprises:

means for determining that ramp direction is downward,

means for determining a cooling breakpoint as a function of said block temperature and a temperature of said coolant, and

means for determining if coolant will be pumped through said ramp cooling channels as a function of said total cooling power and said cooling breakpoint, wherein the determination made by said means for determining if coolant will be pumped through said ramp cooling channels constitutes a ramp cooling decision.

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229. (Previously presented) The apparatus of claim 228, wherein said computing apparatus comprises means for adjusting said theoretical cooling power when said sample temperature in said second sample interval is within an integral band of said target sample temperature after ramping, in order to close out remaining error.

230. (Previously presented) The apparatus of claim 228, wherein said cooling breakpoint is a function of the difference between said block temperature in said first sample interval and said temperature of said coolant fluid in said first sample interval.

231. (Previously presented) The apparatus of claim 219, further comprising means for overshooting the temperature of said sample block above a desired sample temperature, thereby decreasing an upramp time required for said liquid sample mixture to achieve said desired sample temperature.

232. (Previously presented) The apparatus of claim 231, further comprising means for controlling the overshoot such that it is equal to or less than approximately 0.5° C.

233. (Previously presented) The apparatus of claim 219, further comprising means for undershooting the temperature of said sample block below a desired sample temperature, thereby decreasing a downramp time required for said liquid sample mixture to achieve said desired sample temperature.

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234. (Previously presented) The apparatus of claim 233, further comprising means for controlling the undershoot such that it is equal to or less than approximately 0.5° C.

235. (Previously presented) The apparatus of claim 219, wherein said means for determining the temperature of said block in said first sample interval comprises second means for determining the temperature of said block in said first sample interval as a function of at least one temperature of said block in a previous sample interval.

236. (Previously presented) The apparatus of claim 219, further comprising user-controllable means for defining a temperature range such that said computing apparatus will commence timing said hold time when said sample temperature is within said temperature range of said target sample temperature.

237. (Previously presented) The apparatus of claim 219, further comprising an input device for receiving a tube type and a reaction volume, and wherein said computing apparatus comprises means for determining said thermal time constant for a sample tube as a function of the tube type and a sample volume.

238. (Previously presented) The apparatus of claim 219, further comprising means to continually monitor said block sensor and to invoke an abort procedure if block sensor readings are above a maximum desirable temperature for said block by a predetermined number of degrees for a predetermined number of times.

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239. (Previously presented) An apparatus comprising:

a heating and cooling system;

a sample block including at least one well for at least one sample tube containing a known volume of a liquid sample mixture wherein the sample block is capable of thermal contact with the heating and cooling system,

a temperature sensor capable of determining the temperature of said block in a first sample interval, wherein said first sample interval is an interval of time designated as time  $n$ ; and

a computing apparatus to control the heating and cooling system and comprising a program adapted to determine the temperature of a liquid sample mixture as a function of the temperature of said sample block over time by utilizing the relationship:

$$Tsamp_n = Tsamp_{n-1} + (TB_n - Tsamp_{n-1}) * t_{interval}/\tau$$

where  $Tsamp_n$  is equal to the sample temperature in said first sample interval,  $Tsamp_{n-1}$  is a sample temperature in a second sample interval immediately preceding the first sample interval, said second sample interval designated as time  $n-1$ ,  $TB_n$  is equal to the block temperature in said first sample interval,  $t_{interval}$  is a time in seconds between consecutive sample intervals, and  $\tau$  is a function of thermal characteristics of said apparatus.

240. (Previously presented) The apparatus of claim 239, wherein said thermal characteristics comprise a first thermal time constant corresponding to at least one sample tube and a volume of a sample mixture, and a second thermal time constant corresponding to a block temperature sensor thermally coupled to said block, and  $\tau$  equals approximately said first thermal time constant minus said second thermal time constant.

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241. (Previously presented) The apparatus of claim 239, further comprising an input device for receiving user defined setpoints defining a hold time/temperature profile, wherein said computing apparatus includes a controller capable of controlling said heating and cooling system as a function of said user defined setpoints and a sample temperature.

242. (Previously presented) The apparatus of claim 239, wherein the at least one well of the sample block is capable of receiving at least one sample tube containing a volume of liquid sample mixture in the range of from approximately 20 microliters to approximately 100 microliters.

243. (Previously presented) The apparatus of claim 239, further comprising an enclosure for said sample block, said enclosure defining an enclosed ambient atmosphere, and wherein said sample block comprises a central region, an end edge region, and a manifold region, the central region comprises an upper surface, the upper surface contains an array of sample wells for holding the at least one sample tube, the end edge region comprises two end edges at opposite ends of said block which are in thermal contact with said enclosed ambient atmosphere, and the manifold region comprises two manifold edges at opposite sides of said block, wherein each said manifold edge is thermally coupled to a manifold.

244. (Previously presented) The apparatus of claim 243, wherein said heating and cooling system includes a heater having a central heating zone thermally coupled to the central region, an end edge heating zone thermally coupled to the end edge region, and a manifold heating zone thermally coupled to the manifold region.

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245. (Previously presented) The apparatus of claim 244, wherein said computing apparatus is capable of determining an actual heating power to be applied to each said heating zone in said first sample interval, including:

determining a theoretical second power representing the total power to apply to said block in said sample interval, without accounting for power losses,

determining theoretical third powers to be applied to each said zone in said first sample interval as a function of said theoretical second power,

determining power losses by said regions in said first sample interval, and

determining the actual heating power to be applied to each said heating zone as a function of said theoretical third powers and said power losses by said regions.

246. (Previously presented) The apparatus of claim 244, wherein said sample block contains multiple transverse bias cooling channels alternating with multiple transverse ramp cooling channels; said bias and ramp cooling channels being parallel to said upper surface, said system further comprising a pump for constantly pumping chilled coolant through said bias cooling channels and for selectively pumping chilled coolant through said ramp cooling channels, and a valve controlled by said computing apparatus.

247. (Previously presented) The apparatus of claim 246, wherein said computing apparatus is capable of determining a total cooling power to be applied to said block in said first sample interval including:

determining a theoretical cooling power representing the total power to apply to said block in said first sample interval without accounting for power losses,

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determining power losses in said block regions in said first sample interval, and  
determining said total cooling power as a function of said theoretical cooling power and  
said power losses.

248. (Previously presented) The apparatus of claim 247, wherein said computing apparatus is  
capable of:

determining that ramp direction is downward,  
determining a cooling breakpoint as a function of said block temperature and a  
temperature of said coolant, and  
determining if coolant will be pumped through said ramp cooling channels as a function  
of said total cooling power and said cooling breakpoint, wherein the determination constitutes a  
ramp cooling decision.

249. (Previously presented) The apparatus of claim 248, wherein said computing apparatus is  
capable of adjusting said theoretical cooling power when said sample temperature in said second  
sample interval is within an integral band of said target sample temperature after ramping, in  
order to close out remaining error.

250. (Previously presented) The apparatus of claim 248, wherein said cooling breakpoint is a  
function of the difference between said block temperature in said first sample interval and said  
temperature of said coolant fluid in said first sample interval.

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251. (Previously presented) The apparatus of claim 239, wherein said computing apparatus is capable of overshooting the temperature of said sample block above a desired sample temperature, thereby decreasing an upramp time required for said liquid sample mixture to achieve said desired sample temperature.

252. (Previously presented) The apparatus of claim 251, wherein the computing apparatus is capable of controlling the overshoot such that it is equal to or less than approximately 0.5° C.

253. (Previously presented) The apparatus of claim 239, wherein said computing apparatus is capable of undershooting the temperature of said sample block below a desired sample temperature, thereby decreasing a downramp time required for said liquid sample mixture to achieve said desired sample temperature.

254. (Previously presented) The apparatus of claim 253, wherein the computing apparatus is capable of controlling the undershoot such that it is equal to or less than approximately 0.5° C.

255. (Previously presented) The apparatus of claim 239, wherein said computing apparatus is capable of determining the temperature of said block in said first sample interval as a function of at least one temperature of said block in a previous sample interval.

256. (Previously presented) The apparatus of claim 239, further comprising an input device for defining a temperature range such that said computing apparatus will commence timing said hold

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time when said sample temperature is within said temperature range of said target sample temperature.

257. (Previously presented) The apparatus of claim 239, further comprising an input device for receiving a tube type and a reaction volume, and wherein said computing apparatus comprises determining said thermal time constant for a sample tube as a function of the tube type and a sample volume.

258. (New) The apparatus of claim 219, wherein tinterval equals approximately 0.2 seconds.

259. (New) The apparatus of claim 239, wherein tinterval equals approximately 0.2 seconds.